A Cohort Study of Health Care Workers to Assess Nosocomial Transmissibility of Nipah Virus, Malaysia, 1999

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During 1998–1999, an outbreak of Nipah virus encephalitis occurred in Malaysia. To assess the possibility of nosocomial transmission, 338 health care workers (HCWs) exposed and 288 HCWs unexposed to outbreak-related patients were surveyed, and their serum samples were tested for anti-Nipah virus antibody. Needlestick injuries were reported by 12 (3%) HCWs, mucosal surface exposure to body fluids by 39 (11%), and skin exposure to body fluids by 89 (25%). No encephalitis occurred in either group. Three exposed and no unexposed HCWs tested positive by EIA for IgG antibodies. It is likely that these 3 were false positives; no IgM response occurred, and the serum samples were negative for anti-Nipah virus neutralizing antibodies. The risk of nosocomial transmission of Nipah virus appears to be low; however, given the high case-fatality rate and the presence of virus in respiratory secretions and urine of some patients, standard and droplet infection-control practices should be maintained with these patients.

In October 1998, an outbreak of fatal encephalitis occurred among pig farmers living in the Ipoh area of Malaysia, north of Kuala Lumpur [1–3]. The outbreak in Ipoh had ended by February 1999; however, a similar encephalitic illness began among pig workers in the Bukit Pelandok area of the state of Negeri Sembilan. The illness was believed to be Japanese encephalitis until 19 March 1999, when it was discovered that some patients were infected with a new paramyxovirus, which was later named Nipah virus.

Nipah virus appears to be closely related to Hendra virus, which was first identified in Australia and was associated with transmission to humans from infected horses [4, 5]. By June 1999, 265 patients were hospitalized with suspected Nipah virus encephalitis, and 105 (40%) died. About 85% (n = 224) of all patients reported were from Negeri Sembilan State. Many of those hospitalized required mechanical ventilation and were placed in intensive care units. Before the identification of Nipah virus, these patients with encephalitis were not considered to be infectious to health care workers (HCWs), because their illness was believed to be the mosquito-borne Japanese encephalitis. Consequently, HCWs did not use infection-control precautions to protect themselves against contact with or respiratory spread of this virus. The isolation of Nipah virus from the nasopharynx and urine samples of several patients [6] raised concerns that HCWs may have been exposed to the virus. In addition, some encephalitis patients reported no close contact with pigs and presumably were infected from other sources, possibly infected humans [7]. Here we describe a study that looked for evidence of nosocomial transmission of Nipah virus to HCWs caring for hospitalized patients with presumed or documented Nipah virus encephalitis.

Methods

The study was conducted at 3 hospitals that admitted >80% of the patients with suspected Nipah virus encephalitis from 26 December 1998 through 30 April 1999. We identified nurses and doctors exposed to patients hospitalized with outbreak-related encephalitis after 1 March 1999, by reviewing nursing duty rosters (for nurses) and ward rotation schedules (for doctors). Most outbreak-related encephalitis patients (110 [97%] of 113) were admitted after 1 March 1999. Exposure was defined as having provided direct patient care to an encephalitis patient from the Negeri Sembilan State who was admitted after 1 March 1999. We sought to enroll an equal number of unexposed nurses and doctors from wards that did not admit encephalitis patients, to minimize the risk of inclusion...
of HCWs who may have been exposed unknowingly. HCWs from these wards who reported working with encephalitis patients or having worked on wards that admitted patients with encephalitis after October 1998 were excluded from the unexposed group. All pathologists and their assistants in the pathology departments were included in the study and were asked whether they had any contact with the body of an encephalitis patient admitted after 1 March 1999. Study participants completed a questionnaire about types of exposures to patients with encephalitis and work practices. In addition, they were asked to provide 1 (unexposed HCWs) or 2 serum samples (exposed HCWs). The initial serum sample from both unexposed and exposed HCWs was obtained at the time the questionnaire was administered. To ensure that recent infections were not missed, exposed HCWs were asked to provide a second serum sample 3–4 weeks later.

Infection was detected by an EIA for anti-Nipah virus IgM and IgG antibodies. IgM antibodies were detected by using an IgM capture EIA, and IgG antibodies were detected by using an indirect EIA. Hendra virus–derived antigen was used in both assays, because antibodies to Nipah virus react against Hendra virus antigens (CDC, unpublished data). Serum samples that were positive or that gave a borderline positive result for Nipah virus antibodies by the EIA were tested with a neutralization assay, to confirm the specificity of the EIA result. For the neutralization assay, the heat-inactivated serum samples were tested in duplicate in a biosafety level 4 laboratory at dilutions of 1:10–1:640 against a median virus challenge of 30–300 TCID of prototype Nipah virus in Vero E-6 cells. Replication of virus was determined at 6 days by microscopy, to detect syncytial formation, after the cells were fixed with formaldehyde, and cell monolayers were stained with crystal violet. The neutralization titer was considered to be the highest dilution with complete inhibition of syncytial formation.

A standardized questionnaire was developed in English, translated into Bahasa Malay, and administered by public health nurses fluent in both languages. The questionnaire obtained information on demographics, illness, and types of exposures to encephalitis patients or patient body fluids and secretions. A second questionnaire, administered to the exposed cohort at the time of the collection of the second serum sample, obtained information about illnesses, exposures, and activities that had occurred after the administration of the first questionnaire.

Data were entered into an Epi Info 6.02 data file (Centers for Disease Control and Prevention), and differences in responses among unexposed and exposed HCWs were tested for significance by using the $\chi^2$ test. Because the 3 hospitals varied in the level of exposure by both number of patients admitted and the time of first outbreak-related admissions, we examined data from each hospital independently.

### Results

In all, 363 HCWs, pathology workers, and pathology assistants were recruited for the exposed cohort (>98% of HCWs and pathologists that records showed had been exposed to outbreak-associated cases of encephalitis) and 288 HCWs, pathologists, and pathology assistants were recruited for the unexposed cohort. Hospital A had 10 outbreak-related admissions, the first occurring on 2 March 1999; hospital B had 117 outbreak-related admissions beginning on 26 December 1999; and hospital C had 84 outbreak-related admissions after 22 February 1999 (table 1). The exposed and unexposed groups were similar in distribution of jobs, age, sex, and ethnicity. More than 60% of the exposed HCWs reported contact with an encephalitis patient before the institution of infection control measures on 19 March 1999 when Nipah virus was first identified (table 2). Many HCWs reported episodes of a high-risk exposure (e.g., needlestick injury [$n = 12$] or splash of patient body fluids to mucosal membranes [$n = 39$]).

There were no reports of any serious illness, encephalitis, or hospital admission among any HCW or pathology worker. The proportion of HCWs reporting any illness during the month before the study was not statistically significant between exposed and unexposed HCWs (32% vs. 26%, respectively; $P = .12$), nor was the proportion of HCWs who reported a febrile illness (12% vs. 13%, respectively; $P = .87$) statistically significant.

None of the first serum samples from either the exposed or unexposed groups tested positive by EIA for Nipah virus IgG or IgM antibody. Sixty-four nurses and doctors temporarily assigned to hospital 3 were unavailable for a second serum sample; they were on temporary duty at hospital 3 and had returned to their permanent duty station at the time the second serum sample was to be obtained. Most (293 of 299) of the remaining exposed HCWs and pathology workers gave a second serum sample and completed the second questionnaire. Three (1%) of the second serum samples from exposed HCWs and pathology workers were positive for Nipah virus IgG antibodies. It is likely that these 3 were false positives; no IgM response occurred, and the serum samples were negative for anti–Nipah virus neutralizing antibodies. These 3 serum samples were provided by 3 nurses: 1 reported a febrile illness before the first serum sample was obtained, another reported a febrile illness between the 2 serum samples obtained, and 1 reported a mucosal splash exposure. All 3 nurses had cared for outbreak-related encephalitis patients >30 days, compared with 10 days in nurses with negative IgG.

### Discussion

The results of this study of >300 HCWs exposed to patients presumed to be ill with Nipah virus encephalitis suggest that

### Table 1. Date of first presumed Nipah encephalitis admission, number of infected patients admitted, and workers exposed by study hospital.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>First admission</th>
<th>No. of Näipah cases</th>
<th>No. of exposed HCWs</th>
<th>No. of exposed PWs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 March 1999</td>
<td>10</td>
<td>92</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>26 December 1998</td>
<td>117</td>
<td>69</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>22 February 1999</td>
<td>84</td>
<td>177</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>211</td>
<td>338</td>
<td>25</td>
</tr>
</tbody>
</table>

NOTE. HCWs, health care workers, including doctors, nurses, nursing assistants, and phsyiotherapists; PWs, pathologists and pathology assistants.

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Table 2. Exposures reported by health care workers caring for or pathologists performing autopsies on patients with presumed Nipah virus infection.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Doctors (n = 9)</th>
<th>Nurses (n = 269)</th>
<th>Othera (n = 18)</th>
<th>Pathologists and assistants (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient care days, mean</td>
<td>18</td>
<td>10</td>
<td>12</td>
<td>—</td>
</tr>
<tr>
<td>Autopsies, mean no.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4.9</td>
</tr>
<tr>
<td>Specific exposures, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 19 March 1999b</td>
<td>39 (80)</td>
<td>158 (59)</td>
<td>9 (50)</td>
<td>20 (80)</td>
</tr>
<tr>
<td>Needlestick injury</td>
<td>4 (8)</td>
<td>5 (2)</td>
<td>0</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Splash exposurec</td>
<td>7 (14)</td>
<td>26 (10)</td>
<td>3 (17)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Skin exposured</td>
<td>16 (3)</td>
<td>54 (20)</td>
<td>14 (78)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Wore no protective equipment</td>
<td>10 (20)</td>
<td>12 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wore mask most of timee</td>
<td>17 (35)</td>
<td>236 (88)</td>
<td>18 (100)</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Pig exposure</td>
<td>1 (&lt;2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a Nurse assistants, attendants, and physiotherapists.

b After Nipah virus was announced on 19 March 1999, infection control measures implemented included sequestration of suspected Nipah patients in special wards and caps, masks, and shoe covers worn at all times by health care workers in wards and gloves and gowns worn when working directly with patients.

c Reported splash of patient blood or body fluids to eyes, nose, or mouth.

d Reported contact of patient blood or body fluids onto bare skin.

e Reported wearing surgical mask “most of the time” when performing invasive procedures, endotracheal suctioning, or use of bone saw by pathologists.

The risk of nosocomial transmission of Nipah virus is very low. Despite substantial contact with patients with outbreak-related encephalitis (or potentially infectious body fluids from these patients) by many HCWs or pathology workers, none had clinical evidence of infection (i.e., encephalitis or other serious illness), and none had definitive serologic evidence of infection, although the sensitivity of these assays is not completely known. Although 3 HCWs had a positive EIA result for Nipah virus IgG antibodies in their second serum sample, none developed an IgM response or Nipah virus neutralizing antibodies. Thus, it is likely that these 3 serum samples contained antibodies that were not induced by Nipah virus infection but did react against the Hendra virus antigen preparation used in the EIA. The lack of nosocomial transmission of Nipah virus to HCWs is somewhat unexpected, given reports of potentially high-risk exposures; many HCWs cared for patients before they were advised to use contact and respiratory precautions, and a substantial number reported needlestick injuries, splash exposure, and skin exposure to body fluids from encephalitis patients.

The lack of nosocomial transmission is consistent with the fact that most Nipah virus–infected patients had direct contact with pigs [7], and few, if any, were likely to have been infected by contact with household members. Our findings are also consistent with the lack of transmission of Hendra virus to HCWs caring for Hendra virus–infected patients in Australia [8]. This difference in risk of infection between exposure to pigs and humans follows from differences in the extent of infection in the respiratory tract between pigs and humans. Immunohisto logic studies demonstrate high levels of Nipah virus antigen in the lungs and upper respiratory tract of infected pigs, with substantially lower levels of Nipah antigen in these tissues from autopsy specimens from Nipah virus–infected humans [9].

In conclusion, Nipah virus–infected patients do not appear to present a high risk of transmitting the virus to HCWs. However, it is likely that there is some risk for human-to-human transmission, since viral antigens have been detected in human kidney and respiratory tract tissues, and since the virus has been isolated from human urine and respiratory secretion specimens [6]. Given the potential severity of illness, we feel that HCWs should use standard and droplet precautions (e.g., strict attention to good hand washing practices, wearing a mask, and wearing gloves when coming in contact with secretions, excretions, and body fluids of patients) while caring for patients infected with, or likely to be infected with, Nipah virus [10].

Nipah Virus Nosocomial Study Group Members

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Acknowledgments

We acknowledge the helpful assistance of Marty Monroe (Diagnostics Section, Centers for Disease Control and Prevention, Special Pathogens Branch) for performing serologic assays and the Field Investigation Team for administering questionnaires and collecting serum samples.
References


